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EXAMINER	
SKIBINSKY, ANNA	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
12/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,351	GUSTAFSSON ET AL.	
	Examiner	Art Unit	
	ANNA SKIBINSKY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-81 and 101-119* is/are pending in the application.

4a) Of the above claim(s) *109-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-81 and 101-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 8/11/2008 have been fully considered but they are not deemed persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election Restriction

Claims 109-119 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/11/2008.

In the reply filed 8/11/2008, Applicants have stated (Remarks, page 8, ¶3) on the record that the claims 109-119 are patentably distinct from the subject matter of the elected Group XI (original claims 76-81).

In the restriction requirement filed 3/28/2006, Applicant elected Group XI, drawn to a method and computer program produce for identifying nucleotides for variation in nucleic acids encoding protein and from the data developing a sequence activity **model that predicts activity** as a function of nucleotide types and corresponding position in the nucleotide sequence.

Claims 109-119, are drawn to developing a sequence activity **model that predicts a quantity of protein expressed** as a function of nucleotide types and corresponding position in the nucleotide sequence. These claims are therefore

patentably distinct because the method of claims 109-119 is directed to developing a model that has a different mode of operation and effect, wherein the elected model is one that predicts activity of the protein and the non-elected claims 109-119 are to a model that predicts quantity of protein express.

Thus, newly presented claims 109-119 are not drawn to the originally elected invention and are therefore withdrawn from examination.

The election requirement wherein Applicants elected Group XI is still deemed proper and is therefore made FINAL.

Response to Applicants

Amendments to claims 76 and 79 and new claims 101-108 are acknowledged. Claims 76-81 and 101-108 are under examination. Claims 1-75 and 82-100 are cancelled.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 76-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-9 and 14 of copending Application No.11/706034 in view of Hellberg et al. Although the conflicting claims are not identical, they are not patentably distinct from each because it would be obvious to use non-linear terms; e.g. as taught by Hellberg et al. in the sequence activity model in claims 1 and 8 of '034.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants have stated (Remarks, page 8, ¶4) that they will consider the non statutory obviousness-type double patenting rejection when an indication of allowable subject matter is made in either the present application or Application 11/706,034.

A terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) to overcome the instant rejection has not been filed, therefor the rejection is maintained.

Claim Rejections - 35 USC § 101

The instant rejection is maintained from the previous Office action.

1. 35 U.S.C. 101 reads as follows:

2. Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 79-81 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The instant claim are drawn to a carrier wave, per se, and as such reads on the judicial exception of a natural phenomena. The Office's position is that a carrier wave is a form of energy and as such reads on a natural phenomena. (in re Nuijten, 2006; Federal Circuit)

Reply to Arguments

Applicant's arguments filed 8/11/2008 have been fully considered but they are not persuasive.

The instant claims recite a “computer readable medium” and therefore embodies a carrier wave, as disclosed in the instant specification on page 45 wherein a computer program product that includes a computer readable medium is disclosed. Further, page 81 discloses that examples of CRM include “signal transmission media…program may be embodied on a carrier wave or other transport medium”. Therefore, the claims read on carrier waves and are not statutory (see In re Nuijten).

Claim Rejections - 35 USC § 112-2nd paragraph

1. The instant rejection is necessitated by amendments filed 8/11/2008.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 76-78 and 101-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 76, step (e) has been amended to recite "generating a new protein variant library containing one or more of the protein variants in which nucleotides are varied or fixed in order to impact the desired activity". It is now unclear as whether " one or more of the protein variants” refers to the variants in step (a), line 2 or to a possible protein variant encoded from "the reference nucleotide sequence, that are to be varied" recited

in step (d). Because there is no actual step of varying the reference nucleotide sequence of step (d) and encoding the reference nucleotide to make clear that this is "the variant" referred to in step (e), the recitation of "the variant" in step (e) makes it unclear as to which variant is intended.

5. Claim 76, step (f) recites "assaying the new protein variant library to provide activity information **used to** develop a new computational activity model" and step (g) recited “using the new computational algorithmic sequence activity model”. This is vague and indefinite because it is not clear if the activity information recited in step (g) is intended to be used or if "**used to** develop” is a limitation pertaining the actually using the activity information. This ambiguity leads to an indefiniteness as to whether “using a new computational algorithmic sequence activity model” in step (g) is referring to using the model recited in step (f) or to the model in step (b). The model in step (b) might also be considered to be a “new computational algorithmic sequence activity model”. Thus as written, the structure of the iterative loop recited by the claims is open to both embodiments and is therefore vague and indefinite as to which embodiment is intended to carryout the algorithm correctly.

Claim Rejections - 35 USC § 103

6. The rejection of claims 76-81 and 101-108 under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. in view of Voight et al. is withdrawn in view of Applicant’s amendments filed 8/11/2001.

7. The instant rejection is necessitated by amendments filed 8/11/2008.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 76-81 and 101-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (Journal of Medicinal Chemistry, vol. 30 (1987) pages 1126-1135) in view of Schellenberger et al. (PGPub 2002/0155460, claiming priority date of 10/10/2000).

1. The instant claims recite a method for identifying amino acid residues for variation in a protein variant library. The identifying entails the characterization of a training set of protein variant sequences and determining which amino acids in the sequence have the greatest impact on the activity of the sequence.

1. Claim 76(a) recites receiving data characterizing a training set of a protein variant library of systematically varied sequences where the data comprises activity and amino acid sequence for each protein variant in the training set.

2. Hellberg et al. teach the measurement of various properties of amino acids in a peptide (page 1128, col. 1, lines 6-4 from bottom) and data from compounds with known biological activity, a training set, used to construct a model (page 1130, col. 1, lines 3-7 from bottom).

3. Claim 76 (b) recites developing a sequence activity model that predicts activity as a function of amino acid residue type and position in the sequence.

4. Hellberg et al. teach a model constructed from the training set that is used to predict structures that improve biological activity (page 1130, col. 1, lines 1-7 from bottom). The chemical structure is quantified by varying amino acids at certain positions. The structure activity relationship is analyzed with regard to introduction or deletion of features at various positions in the peptides (page 1127, col. 2, lines 6-10 from bottom; page 1128, col. 1, lines 37-45; and col. 2, lines 1-19).

2. Claim 76, step (c) recites ranking positions in a nucleotide sequence or types at specific positions in order of impact on the desired activity.

3. Hellberg et al. teach using the model to quantify peptide analogues where each varied amino acid is described by variables (page1128, col. 2, section “II. Peptide Description”). A test matrix is taught where the amino acid with the highest absolute z values are chose to be included in a test series (page 1129, col. 2, ¶ 7 and Table V) and shows a test series of 16 peptides with four amino acid positions that were varied.

4. Claim 76, step (d) recites using the ranking to identify one or more nucleotides, in the reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

5. Hellberg et al. teach varying positions 2 and 4 in Pepstatin Analogues (Example III, page 1133, col. 1) wherein the calculated activity of seven analogues are plotted as function of activity in Figure 3.

6. Claim 76(e) recites generating on or more of the protein variants encoded by the reference nucleotide sequence with the identified nucleotides that are varied or fixed.

7. Hellberg et al. teach generating the analogues having the identified amino acid residues varied in order to impact desired activity, as shown in Figure 3. Furthermore, Hellberg et al. teach the design a series of analogues based on the analysis done with the activity model (page 1128, col. 1., lines 45-49; and page 1129, col. 2, section "Design Example").

5. As in claim 77, Hellberg et al. further teach that their model is not limited to amino acid sequences but that a design for only coded amino acids, a set of codon sequences (i.e. nucleotides in DNA) can be constructed that corresponds to a set of designed peptide fragments (page 1135, col. 2, ¶2).

6. Hellberg et al. teach performing steps (a)-(c) using activity and sequence data from protein variants, page 1135, col 2, ¶ 2), as in claim 107.

7. Hellberg et al do not teach generating a new protein variant library, assaying the new protein library to develop a new computational algorithmic sequence activity model and using the new model to identify nucleotides in a reference sequence that are to be

varied as in claim 76, steps (e) to (g). Hellberg et al. using a computer program product to carryout the steps of the method, as in claims 79-81. Hellberg et al. do not teach a library of protein mutants generated from nucleic acid sequences and using directed evolution methods such as gene synthesis, mutagenesis, and recombination-based screening where nucleotide sequences are used to generate protein libraries based on the prediction of the activity model, as in claims 78, 101-106 and 108.

8. Claim 76, step (e) recites generating a new protein variant library containing at least one of the protein variant in which the identified nucleotides are varied or fixed to impact desired activity.

9. Schellenberger et al. teach a “probability matrix’ (another form of sequence activity model) that provides an estimate that a given residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest (par. [0059]) and constraint vectors that reflect the likelihood that a specific mutation at each amino acid position of a protein will improve or effect the desired activity (par. [0073]). Schellenberger et al. also teach ranking amino acids (par. [0065])

10. Schellenberger et al. teach construction of libraries by randomizing codons at specific locations that have been identified (par. [0087] to [0090]).

11. Claim 76, step (f) recites assaying the new protein variant library to provide activity information used to develop a new computational algorithmic sequence activity model.

12. Schellenberger et al. teach generating a library and screening the library of proteins for members with desired activity and deriving information from the screening

which is then used to design an improved probability matrix and constraint vectors (i.e. develop a new computational algorithmic sequence activity model) for a next iteration of mutagenesis and library construction (par. [0099]).

13. Claim 76, step (g) recites using the new computational algorithmic sequence activity model to identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

14. Schellenberger et al. teach the iteration of their method using a new activity model, wherein their activity model is the probability matrix and constraint vectors which estimates that a given residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest (par. [0059]) and constraint vectors that reflect the likelihood that a specific mutation at each amino acid position of a protein will improve or effect the desired activity (i.e. identify one or more nucleotides in a new reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity).

15. Schellenberger et al. teach that molecules with desired activity can be propagated and subjected to rounds of mutagenesis and selection (par. [0008]). Schellenberger et al. generating libraries of molecules including nucleic acids by expressing in host cells and screening molecules for desired properties, as in claim 78.

16. Schellenberger et al. teach the use of computers (i.e. Computer program product) to carryout sequence activity calculations for determining which residue will provide a desired activity in a biological polymer (e.g. polynucleotide) of interest, (par. [0066], [0071], and [0080]), as required in claims 79-91.

17. Schellenberger et al. teach construction of libraries by randomizing codons at specific locations that have been identified (par. [0087] to [0090]), generating libraries of proteins from the nucleic acid sequences and screening the libraries of proteins for members with desired activity (par. [0099]), as in claim 101.

18. Schellenberger et al. teach mutation of genes to diversify polymeric biological molecules and create a library of genes used to express proteins (par. [0005] to [0006]), as in claim 102.

19. Schellenberger et al. teach mutagenesis (par. [0006]), as in claim 103.

20. Schellenberger et al. teach recombination-based diversity generation mechanism (par. [0007]), as in claim 104.

21. Schellenberger et al. teach further screening of newly generated protein variant library to identify variants having desired activity (Abstract, par. [0012], [0035], [0099]), as in claim 105.

22. Schellenberger et al. teach sequencing the library (par. [0099]) ad using sequence information to introduce diversity into a protein of interest (par. [0007]), and characterizing the sequence (par. [0021]) and PCR for sequencing (par. [0094]), as in claim 106.

23. Schellenberger et al. teach codon based mutagenesis (par. [0087]) and a codon by codon technique using mixtures of activated trinucleotides at the positions to be substituted (par. [0091]), as in claim 108.

24. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the sequence activity model (i.e.

QSAR) of Hellberg et al. to in the iterative method for generating a protein variant library with the as taught by Schellenberger et al. One of ordinary skill in the art would have been motivated to use the activity model of Hellberg et al. with the method of creating libraries of biological polymers as taught by Schellenberger et al. because Schellenberger et al teach the need for synthetically screening possible permutations in a polymeric biological molecule such as a polynucleotide (par. [0004]). One of skill in the art would have had a reasonable expectation of success at utilizing the structure activity model of Hellberg et al. with the generation of protein libraries using expression of protein sequences via gene synthesis, mutagenesis and recombination as taught by Schellenberger et al. because Schellenberger et al. also teaches the use of QSARs (par. [0104]).

Response to Arguments

Applicant's arguments with respect to claims 76-81 and 101-108 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anna Skibinsky

/Lori A. Clow/
Primary Examiner, Art Unit 1631